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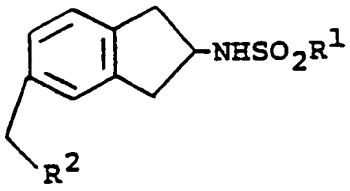
Claim for the following Contracting State: ES + GR.

(54) Indan derivatives and process for preparation thereof.

(57) Indan derivatives of the formula:



(I)

wherein R^1 is substituted or unsubstituted phenyl, naphthyl or sulfur-containing heterocyclic group, and R^2 is hydroxymethyl or a group of the formula: $-CO-N(R^3)-R^4$

wherein R^3 is hydrogen atom or lower alkyl and R^4 is cycloalkyl, lower alkoxycarbonyl-phenyl, carboxy-phenyl, nitrogen-containing heterocyclic group, lower alkyl, or lower alkyl having a substituent selected from lower alkoxycarbonyl, carboxy, lower alkoxycarbonyl-phenyl, carboxy-phenyl, lower alkoxycarbonyl-cycloalkyl and carboxy-cycloalkyl, or a pharmaceutically acceptable salt thereof, which are useful as a platelet aggregation-inhibiting agent and as an agent for the treatment, amelioration and/or prophylaxis of a variety of thrombosis or embolism, coronary and cerebral vascular smooth muscle vellication, asthma, and the like, processes for the preparation thereof, and pharmaceutical composition containing said compound as an active ingredient.

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Another preferred examples of the compounds of the invention are those of the formula (I) wherein R^1 is a (C_1-C_5)alkyl-phenyl, a (C_1-C_5)alkoxy-phenyl, a halogenophenyl, trifluoromethylphenyl, nitrophenyl, or naphthyl, R^3 is hydroxymethyl or a group of the formula:

$$-CO-\overset{\overset{R^3}{|}}{N}-R^4$$

wherein R^3 is hydrogen atom or a (C_1-C_5)alkyl, and R^4 is carboxy phenyl, tetrazolyl, a (C_1-C_5)alkyl, a (C_2-C_6)alkoxycarbonyl-(C_1-C_5)alkyl or a carboxy-(C_1-C_5)alkyl.

More preferred examples of the compounds of the invention are those of the formula (I) wherein R^1 is a halogenophenyl, and R^2 is a group of the formula:

$$-CO-\overset{\overset{R^3}{|}}{N}-R^4$$

wherein R^3 is hydrogen atom and R^4 is carboxyphenyl, a (C_2-C_4)alkoxycarbonyl-(C_1-C_5)alkyl or a carboxy-(C_1-C_5)alkyl.

Further preferred examples of the compounds of the invention are those of the formula (I) wherein R^1 is chlorophenyl, and R^2 is a group of the formula:

$$-CO-\overset{\overset{R^3}{|}}{N}-R^4$$

wherein R^3 is hydrogen atom, and R^4 is carboxyphenyl or a carboxy-(C_1-C_3)alkyl.

Most preferred examples of the compounds of the invention are those of the formula (I) wherein R^1 is chlorophenyl, and R^2 is a group of the formula:

$$-CO-\overset{\overset{R^3}{|}}{N}-R^4$$

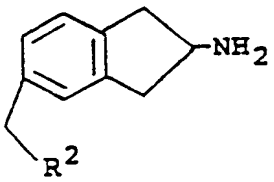
wherein R^3 is hydrogen atom, and R^4 is carboxyethyl or carboxypropyl.

The compounds (I) of the invention may exist in the form of two or four optically active isomers due to one or two asymmetric carbon atom(s), and this invention includes these optically active isomers and a mixture thereof.

According to this invention, the compounds (I) or salts thereof can be prepared by various processes as mentioned below.

Process A

The compounds (I) can be prepared by condensing a 2-aminoindan derivative of the formula:



(II)

wherein R^2 is as defined above, or a salt thereof with a sulfonic acid compound of the formula:

R^1SO_3H (III)

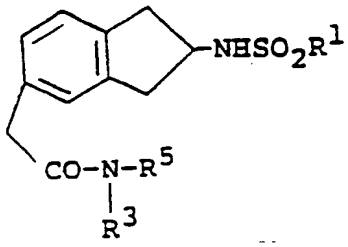
wherein R^1 is as defined above, or a reactive derivative thereof.

The condensation reaction of the aminoindan (II) or a salt thereof (e.g. a mineral acid salt or an organic acid salt) and the sulfonic acid compound (III) or a reactive derivative thereof can be carried out in the presence or absence of an acid acceptor. The reactive derivative of the compound (III) includes any conventional reactive derivative, for example, the corresponding sulfonyl halide. The acid acceptor includes any conventional agents, for example, alkali metal carbonates, alkali metal hydrogen carbonates, trialkylamines, pyridine, and the like. The reaction is preferably carried out in a suitable solvent (e.g. water, ethyl acetate) at a temperature of 0 to 200°C.

Process B

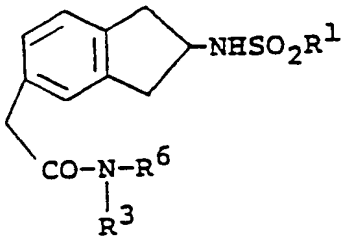
The compounds of the formula (I) wherein R^2 is hydroxymethyl, i.e. the compounds of the formula (I-a):

i.e. the compounds of the formula (I-c):



(I-c)

wherein R^5 is carboxy-phenyl group or a lower alkyl group having a substituent selected from carboxy group, carboxy-phenyl group and a carboxy-cycloalkyl group, and R^1 and R^3 are as defined above, can be prepared by hydrolyzing a compound of the formula (I-d):



(I-d)

wherein R^6 is a lower alkoxycarboxy-phenyl group or a lower alkyl group having a substituent selected from a lower alkoxycarbonyl group, a lower alkoxycarboxy-phenyl group and a lower alkoxycarbonyl-cycloalkyl group, and R^1 and R^3 are as defined above.

The hydrolysis of the compound (I-d) can be carried out by a conventional method, for example, by treating the compound with an alkali agent or an acid. Examples of the alkali agent are alkali metal hydroxides, and examples of the acid are mineral acids. The hydrolysis is preferably carried out in an appropriate solvent (e.g. water, a lower alcohol) at a temperature of 0 to 30°C.

All of the above reactions in Processes A to D proceed without racemization, and hence, when an optically active compounds are used as the starting materials, the desired compounds (I) can be obtained in the optically active form.

The starting compound (II) wherein R^2 is hydroxymethyl group can be prepared, for example, by the steps of condensing a 2-(N-protected amino)indan with a lower alkyl ester of the compound of the formula:

Z-CH(X)-COOH (VI)

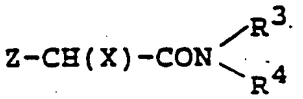
wherein X is a halogen atom and Z is a lower alkylmercapto group or a substituted or unsubstituted phenylmercapto group, removing the substituted mercapto group from the product to give a lower alkyl [2-(N-protected amino)indan-5=yl]acetate, hydrolyzing the product by conventional method, reducing the thus-obtained [2-[N-protected amino)indan-5-yl]acetic acid, and then removing the protecting group from the product by conventional method.

On the other hand, the compound (II) wherein R^2 is a group of the formula:

-CO-N(R^3)-R^4

can be prepared, for example, by the steps of

(a) condensing a 2-(N-protected amino)indan with a compound of the formula:



(VII)

wherein R^3, R^4, X and Z are as defined above, removing the substituted mercapto group from the product

Inhibiting effect on arachidonic acid-induced pulmonary embolism (in vivo):

A test compound in an aqueous carboxymethyl-cellulose solution (20 ml/kg) was orally administered to ddy-male mice fasted overnight. Three hours later, arachidonic acid (125 mg/kg) was injected to the tail vein of mice to induce pulmonary embolism, and the recovery time (minute) of locomotive activity of the mice was compared with that of a control group of mice to which a 0.25 % aqueous CMC solution was administered instead of the test compound solution. The inhibiting effect of each test compound on arachidonic acid-induced pulmonary embolism was estimated in terms of the dose required to shorten the recovery time by at least 15 % as compared with the control group. The results are shown in Table 1.

Table 1

Test compound No.*	Inhibiting effect on arachidonic acid-pulmonary embolism (in vivo) (mg/kg)
Compounds of this invention	
1	0.03
2	0.03
Control	30

*) Chemical name of test compounds are as follows.

Compd. No.	Chemical name
1:	Sodium 3-[[2-[(4-chlorophenyl)sulfonylamino]-indan-5-yl]acetylamino]-n-propionate
2:	Sodium 4-[[2-[(4-chlorophenyl)sulfonylamino]-indan-5-yl]acetylamino]-n-butyrate
Control:	4-(2-Benzenesulfonylaminoethyl)phenoxyacetic acid (a compound disclosed in Thrombosis Research, 35, 379 - 395, 1984)

Example 1

(1) (2-Formylaminoindan-5-yl)acetic acid (219 mg) and carbonyldiimidazole (162 mg) are mixed with stirring in a mixed solvent of tetrahydrofuran-methylene chloride under ice cooling and the mixture is stirred at room temperature for one hour, and to the reaction mixture are added methyl β-aminopropionate hydrochloride (140 mg) and triethylamine (100 mg), and the mixture is stirred at room temperature for 2 hours. After the reaction, methanol is added to the mixture, and the solvent is distilled off under reduced pressure. The residue is separated and purified by silica gel column chromatography (solvent, chloroform - methanol = 19 : 1) and then recrystallized from ethyl acetate - n-hexane to give methyl 3-[(2-formylaminoindan-5-yl)acetylamino]-n-propionate (238 mg). m.p. 108 - 110°C

(2) The above product (200 mg) is dissolved in 5 % methanol-hydrochloric acid, and the mixture is stirred at room temperature for 24 hours. After the reaction, the solvent is distilled off, and the residue is recrystallized from methanol - diethyl ether to give methyl 3-[(2-aminoindan-5-yl)acetylamino]-n-propionate hydrochloride (152 mg) as colorless needles. m.p. 195 - 197°C

(3) A mixture of the free base of the above product (138 mg), 4-chlorophenylsulfonyl chloride (106 mg), potassium carbonate (138 mg) and ethyl acetate (10 ml) -water (5 ml) is stirred at room temperature for one hour. After the reaction, the organic layer is taken, washed, dried, and then distilled to remove the solvent. The residue is recrystallized from ethyl acetate - n-hexane to give methyl 3-[[2-[(4-chlorophenyl)sulfonylamino]indan-5-yl]acetylamino]-n-propionate (200 mg).

m.p. 147 - 150°C,

MS (m/e): 450 (M^+),

and the residue is dissolved in chloroform. The solution is washed with saturated aqueous saline solution, dried, and then the solvent is distilled off. The residue is separated and purified by silica gel column chromatography (solvent, chloroform : methanol = 19 : 1) and recrystallized from ethyl acetate - n-hexane to give methyl 3-[(2-formylaminoindan-5-yl)acetylamino-n-propionate (1.54 g) as colorless crystals. m.p. 108 - 110°C

(3) To a solution of the above product (2 g) in methanol is added 5 % hydrochloric acid - methanol, and the mixture is reacted at room temperature for 24 hours. The solvent is distilled off from the reaction mixture, and the residue is crystallized from isopropyl ether - diethyl ether to give methyl 3-[(2-aminoindan-5-yl)acetylamino]-n-propionate hydrochloride (1.52 g) as colorless needles. m.p. 195 - 197°C

(4) The free base of the above product (2.76 g) is added to a mixture of ethyl acetate (200 ml) and saturated aqueous sodium hyrogen carbonate solution (100 ml) with stirring, and thereto is further added 4-chlorophenylsulfonyl chloride (2.11 g), and the mixture is stirred at room temperature for 1.5 hour. The ethyl acetate layer is separated, dried, and then the solvent is distilled off under reduced pressure. The residue is crystallized from ethyl acetate - n-hexane to give methyl 3-[[2-[(4-chlorophenyl)sulfonylamino]indan-5-yl]acetylamino]-n-propionate (4.06 g) as colorless needles. m.p. 147 -150°C

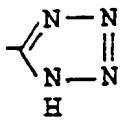
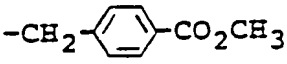
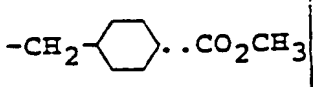
Example 5

To a solution of methyl 4-[(phenylthio)acetylamino]-n-butyrate (6.42 g) in methylene chloride (20 ml) is added dropwise a solution of sulfuryl chloride (3.42 g) in methylene chloride (10 ml). Said dropwise addition is carried out under argon atmosphere with ice-cooling for 10 minutes. The mixture is stirred at the same temperature for one hour. The solvent is distilled off, and the residue is dissolved in methylene chloride (40 ml). 2-Formylaminoindan (3.22 g) is added to the solution and a solution of stannic chloride (11.5 g) and nitromethane (2.75 g) in methylene chloride (20 ml) are added thereto below 10°C for 15 minutes, and the mixture is stirred at room temperature for 8 hours. After the reaction, water (30 ml) is added to the mixture, and the mixture is stirred for 20 minutes. Chloroform (30 ml) is added to the mixture, and the mixture is washed with 10 % hyrochloric acid and dried. The solvent is distilled off, and the residue is dissolved in acetic acid (50 ml). Zinc dust (1.3 g) is added to the solution under reflux, and the mixture is refluxed for 15 minutes. After cooling, zinc dust is removed by filtration, and the solvent is distilled off, and the residue is dissolved in chloroform (100 ml). The solution is washed with an aqueous saline solution containing potassium carbonate (1 g), dried, and then the solvent is distilled off. Ethyl acetate (30 ml) is added to the residue, and the mixture is extracted with water. The solvent is distilled off, and 12.5 % hydrogen chloride-methanol solution (80 ml) is added to the residue, and the mixture is stirred at room temperature for 17.5 hours. The solvent is distilled off, and the residue is dissolved in a mixture of water (30 ml) and toluene (25 ml). Potassium carbonate (5.03 g) and 4-chlorophenylsulfonyl chloride (3.39 g) are added to the solution, and the mixture is stirred.. After the reaction, the mixture is extracted with a mixture of ethyl acetate and tetrahydrofuran, and the extract is washed with an aqueous saline solution, and dried. The solvent is distilled off, and the residue is recrystallized from a mixture of methanol and ethere to give methyl 4-[[2-[(4-chlorophenyl)sulfonylamino]indan-5-yl]acetylamino]-n-butyrate (4.53 g) as colorless powder.
m.p. 126.5 - 127.5°C

Examples 6 to 23

In the same manner as described in any one of Examples 1 to 5, the corresponding starting compounds are treated to give the compounds of the following Table 2.

Table 2 (Continue)

Ex. No.	Compound A			Physical properties, etc.
	R^1	R^3	R^4	
10		H	$-C_2H_5$	m.p. 148-150°C (recryst. from ethanol-n-hexane) MS (m/e): 392 (M^+) IR ν_{max}^{nujol} cm^{-1}: 3310, 3270, 1640
11	"	H	$-CH(CH_3)_2$	m.p. 165-166°C (recryst. from ethanol-n-hexane) MS (m/e): 406 (M^+) IR ν_{max}^{nujol} cm^{-1}: 3360, 3080, 1640
12	"	H	$-C(CH_3)_3$	m.p. 148-149°C (recryst. from ethanol-n-hexane) MS (m/e): 420 (M^+) IR ν_{max}^{nujol} cm^{-1}: 3380, 3180, 1650
13	"	H		m.p. 263-264°C (recryst. from ethyl acetate) MS (m/e): 433 ($M^+ + 1$) IR ν_{max}^{nujol} cm^{-1}: 3260, 3220, 1700, 1625 Sodium salt: m.p. 204-209°C (dec.)
14	"	H		m.p. 151-153.5°C (recryst. from ethyl acetate-n-hexane) MS (m/e): 515 ($M^+ + 3$) IR ν_{max}^{nujol} cm^{-1}: 3215, 3150, 1730, 1720, 1635
15	"	H		m.p. 147-150°C (recryst. from ethyl acetate-n-hexane) MS (m/e): 521 ($M^+ + 3$) IR ν_{max}^{nujol} cm^{-1}: 3360, 3160, 1735, 1640

to be continued -

Table 2 (Continue)

Ex. No.	Compound A			Physical properties, etc.
	R^1	R^3	R^4	
21		H	$-(CH_2)_3CO_2CH_3$	m.p. 129-130°C (recryst. from ethyl acetate-isopropyl ether) MS (m/e): 499 ($M^+ + 1$) IR ν_{max}^{nujol} cm^{-1}: 3370, 3140, 1730, 1643
22		H	"	m.p. 118-120°C (recryst. from ethyl acetate-n-hexane) MS (m/e): 511 ($M^+ + 3$) and 509 ($M^+ + 1$) IR ν_{max}^{nujol} cm^{-1}: 3360, 3295, 3150 (sh), 3090, 1722, 1650
23		H	"	m.p. 95-99°C (recryst. from ethyl acetate-n-hexane) MS (m/e): 431 (M^+) IR ν_{max}^{nujol} cm^{-1}: 3260, 3170, 3090, 1720

Example 24

(1) A mixture of methyl (2-aminoindan-5-yl)acetate hydrochloride (2.43 g), potassium carbonate (5.52 g), water (60 ml), ethyl acetate (60 ml) and 4-chlorophenylsulfonyl chloride (2.11 g) is stirred at room temperature for one hour. The ethyl acetate layer is separated from the reaction mixture, washed with aqueous saline solution, dried, and distilled under reduced pressure to remove the solvent. The resulting crude product is recrystallized from a mixture of ethyl acetate and n-hexane to give methyl [2-[(4-chlorophenyl)sulfonylamino]indan-5-yl]acetate (3.02 g).

m.p. 91 - 92°C

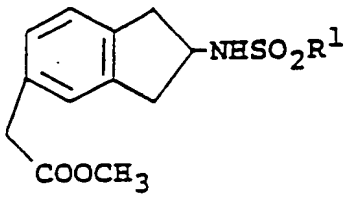
MS (m/e): 381 ($M^+ + 2$), 379 (M^+)

IR ν_{max}^{nujol} cm^{-1}:

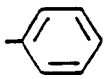
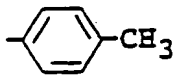
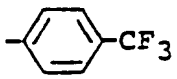
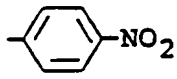
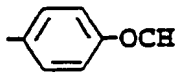
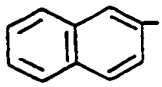
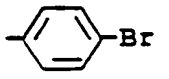
3620, 1725

(2) To a solution of the above product (3.0 g) in methanol (40 ml) is added 1N aqueous sodium hydroxide (20 ml), and the mixture is stirred at room temperature for one hour and distilled under reduced pressure to remove the solvent. The residue is dissolved in water and adjusted to about pH 1 with 10 % hydrochloric acid and then extracted with ethyl acetate. The extract is dried and distilled under reduced pressure to remove the solvent. The resulting crude product is recrystallized from a mixture of ethyl acetate and n-hexane to give

Table 3

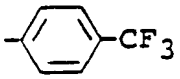
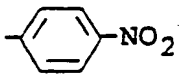
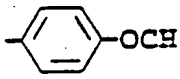
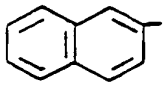
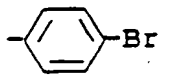
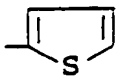


(B)

Compound B R^1	Physical properties, etc.
	m.p. 92-93.5°C *1 MS (m/e): 345 (M^+) IR ν_{max}^{nujol} cm^{-1}: 3300, 1725
	m.p. 102-104°C *1 MS (m/e): 359 (M^+) IR ν_{max}^{nujol} cm^{-1}: 3280, 1740
	m.p. 111-112°C *1 MS (m/e): 413 (M^+) IR ν_{max}^{nujol} cm^{-1}: 3290, 1740
	m.p. 105-106°C *1 MS (m/e): 390 (M^+) IR ν_{max}^{nujol} cm^{-1}: 3280, 1720
	m.p. 108-110°C *1 MS (m/e): 375 (M^+) IR ν_{max}^{nujol} cm^{-1}: 3270, 1735
	m.p. 85-87°C *1 MS (m/e): 395 (M^+) IR ν_{max}^{nujol} cm^{-1}: 3270, 1730
	m.p. 87-89°C *2 MS (m/e): 424 ($M^+ + 1$) IR ν_{max}^{nujol} cm^{-1}: 3290, 3250, 1720

- to be continued -

Table 4 (Continue)

Compound C R^1	Physical properties, etc.
	m.p. 161-162°C *1 MS (m/e): 399 (M^+) IR ν_{max}^{nujol} cm^{-1}: 3265, 1695
	m.p. 173-174°C *1 MS (m/e): 376 (M^+) IR ν_{max}^{nujol} cm^{-1}: 3285, 1700
	m.p. 154-155°C *1 MS (m/e): 361 (M^+) IR ν_{max}^{nujol} cm^{-1}: 3270, 1690
	m.p. 153-155°C *1 MS (m/e): 381 (M^+) IR ν_{max}^{nujol} cm^{-1}: 3270, 1705
	m.p. 167-168.5°C *1 MS (m/e): 410 (M^+ + 1) IR ν_{max}^{nujol} cm^{-1}: 3265, 1698
	m.p. 104-106°C *1 MS (m/e): 337 (M^+) IR ν_{max}^{nujol} cm^{-1}: 3280, 1705

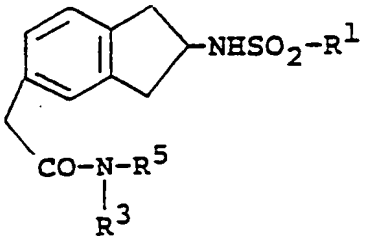
*1) The same as in Table 3
*3) Recrystallized from diethyl ether-n-hexane

(3) In the same manner as described in Example 24-(3), the products obtained in Paragraph (2) and methyl 3-aminopropionate (or methyl 4-aminobutyrate) are treated to give the same compounds as in Examples 16 to 23.

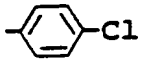
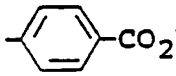
Example 33

A mixture of methyl 3-[[2-[(4-chlorophenyl)sulfonylamino]indan-5-yl]acetylamino]-n-propionate (720 mg), 1N aqueous sodium hydroxide (3 ml) and methanol (10 ml) is stirred at room temperature for 3 hours and then, the solvent is distilled off under reduced pressure. The residue is dissolved in water, and the solution is adjusted to pH 1 with 10 % hydrochloric acid and is extracted with ethyl acetate. The extract is washed with aqueous saline solution, dried and then distilled under reduced pressure to remove the solvent. The resulting crude crystals are recrystallized from ethyl acetate - n-hexane to give 3-[[2-[(4-chlorophenyl)sulfonylamino]indan-5-yl]acetylamino]-n-propionic acid (656 mg, yield 94 %) as colorless crystals.
m.p. 150 - 153°C
MS (m/e): 245 (M^+ - 191)

Table 5

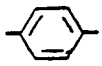
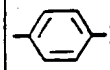


(D)

Ex. No.	Compound D			Physical properties, etc.
	R^1	R^3	R^5	
34		H	$-CH_2CO_2H$	m.p. 182-185°C (recryst. from ethyl acetate) MS (m/e): 231 (M^+ - 191) IR ν_{max}^{nujol} cm^{-1}: 3390, 3265, 1720, 1615 Sodium salt: m.p. 250-253°C (dec.)
35	"	H	$-(CH_2)_3CO_2H$	m.p. 123.5-125.5°C (recryst. from THF-isopropyl ether) MS (m/e): 450 (M^+) IR ν_{max}^{nujol} cm^{-1}: 3270, 3160, 1700, 1620, 1150 Sodium salt: m.p. 196.1°C (dec.)
36	"	H		m.p. 258.5-260.5°C (recryst. from THF-isopropyl ether) MS (m/e): 485 (M^+ + 1) IR ν_{max}^{nujol} cm^{-1}: 3320, 1670 Sodium salt: m.p. 305-311°C (dec.)
37	"	H		m.p. 227.5-229.5°C MS (m/e): 501 (M^+ + 3) IR ν_{max}^{nujol} cm^{-1}: 3300, 2400-2800, 1700, 1682, 1640

- to be continued -

Table 5 (Continue)

Ex. No.	Compound D			Physical properties, etc.
	R^1	R^3	R^5	
44		H	$-(CH_2)_3CO_2H$	m.p. 150-152°C (recryst. from ethanol-n-hexane) MS (m/e): 485 (M^+ + 1) IR ν_{max}^{nujol} cm^{-1}: 3320, 3280, 1720, 1650 Sodium salt: m.p. 197-199°C
45		H	"	m.p. 122.5-125°C (recryst. from isopropanol-ethyl ether-water) MS (m/e): 497 (M^+ + 3), 495 (M^+ + 1) IR ν_{max}^{nujol} cm^{-1}: 3270, 3170, 3090, 1698 Sodium salt: m.p. 197-200°C
46		H	"	m.p. 128-131°C (recryst. from isopropanol-ethyl acetate-ethyl ether) MS (m/e): 417 (M^+ + 1) IR ν_{max}^{nujol} cm^{-1}: 3270, 3170, 3080, 1700 Sodium salt: m.p. 153-157°C

Example 47

In the same manner as described in Examples 24 and 33, methyl (2-aminoindan-5-yl)acetate hydrochloride, 4-chlorophenylsulfonyl chloride and methyl N-methyl-β-amino-propionate hydrochloride are treated to give 2-[N-[2-[(4-chlorophenyl)sulfonylamino]indan-5-yl]acetyl-N-methylamino]acetic acid.
MS (m/e): 436 (M^+)

IR ν_{max}^{nujol} (cm^{-1}):

3500, 3200, 1720, 1630
Sodium salt:
m.p. 204 - 205°C (dec.)

Example 48

A mixture of [2-(4-chlorophenyl)sulfonylamino]indan-5-yl]acetic acid (987 mg), thionyl chloride (2 ml), tetrahydrofuran (10 ml) and methylene chloride (10 ml) is refluxed for 2 hours. After the reaction, the solvent is distilled off under reduced pressure. The residue is dissolved in tetrahydrofuran (8 ml) (this solution is

ml) are mixed, and the mixture is refluxed with stirring for 3 hours. After the reaction, the solvent is distilled off under reduced pressure. The residue is dissolved in methylene chloride (15 ml), and the solution is added dropwise to a mixture of methyl 3-aminopropionate hydrochloride (837 mg), triethylamine (1.00 g) and methylene chloride (30 ml) under ice-cooling. After stirring the mixture at room temperature for 3 hours, the reaction mixture is distilled under reduced pressure to remove the solvent. Ethyl acetate and water are added to the residue, and the mixture is extracted with ethyl acetate. The extract is washed with 10 % hydrochloric acid, saline solution and aqueous sodium bicarbonate solution in this order, dried and then distilled under reduced pressure to remove the solvent. The residue is recrystallized from a mixture of methanol, hexane and isopropyl ether to give methyl (-)-3-[[2-[(4-chlorophenyl)sulfonylamino]indan-5-yl]acetylamino]-n-propionate (1.138 g).
m.p. 110-113°C

IR ν_{max}^{nujol} (cm^{-1}):

3390, 3170, 1725, 1650
$[\alpha]_D^{20}$ -8.52° (c = 0.563,methanol)

(4) A mixture of the above product (992 mg), 1N aqueous sodium hydroxide (4.4 ml) and methanol (8.8 ml) is stirred at room temperature for 2 hours. The mixture is acidified with 10 % hydrochloric acid and extracted with ethyl acetate. The extract is washed with water, dried and distilled under reduced pressure to remove the solvent. The resulting crude crystals are recrystallized from a mixture of ethyl acetate and hexane to give (-)-3-[[2-[(4-chlorophenyl)sulfonylamino]indan-5-yl]acetylamino]-n-propionic acid (821 mg).
m.p. 141 - 142°C

IR ν_{max}^{nujol} (cm^{-1}):

3320, 3260, 1695, 1650
$[\alpha]_D^{20}$ -8.45° (c = 0.201, methanol)

Examples 51 to 53

(1) In the same manner as described in Examples 50-(1), methyl (+)-(2-aminoindan-5-yl)acetate (+)-dibenzoyl-D-tartaric acid salt and 4-chlorophenylsulfonyl chloride are treated to give methyl (+)-[2-[(4-chlorophenyl)sulfonylamino]indan-5-yl]acetate.
m.p. 80 - 82°C

IR ν_{max}^{nujol} (cm^{-1}):

3290, 3260, 1725
$[\alpha]_D^{20}$ +4.76° (c = 1.049, $CHCl_3$)

(2) In the same manner as described in Example 50-(2), methyl (+)-[2-[(4-chlorophenyl)sulfonylamino]indan-5-yl]acetate is treated to give (+)-[2-[(4-chlorophenyl)sulfonylamino]indan-5-yl]acetic acid.
m.p. 154 - 155°C

IR ν_{max}^{nujol} (cm^{-1}):

1700
$[\alpha]_D^{20}$ +9.16° (c = 0.513, methanol)

(3) In the same manner as described in Example 50-(3), (-)- or (+)-[2-[(4-chlorophenyl)sulfonylamino]indan-5-yl]acetic acid and methyl 3-aminopropionate or methyl 4-aminobutyrate are treated to give the following compounds.

(i) methyl (+)-3-[[2-[(4-chlorophenyl)sulfonylamino]indan-5-yl]acetylamino]-n-propionate
m.p. 110 - 113°C

sodium hydrogen carbonate solution and saline solution, dried and then distilled under reduced pressure to remove the solvent. The residue is purified by silica gel column chromatography (solvent, chloroform) to give 2-[2-[(4-chlorophenyl)sulfonylamino]indan-5-yl]ethanol (542 mg) as colorless crystals.
m.p. 71 - 76°C
MS (m/e): 351 (M^+)

IR ν_{max}^{nujol} cm^{-1}:

3500, 3150 (broad)

Reference Example 1

(1) To a solution of 2-aminoindan (19.95 g) in tetrahydrofuran is added an solution of 2M acetic acid-formic acid anhydride in tetrahydrofuran under ice cooling, and the mixture is reacted at room temperature. To the reaction mixture is added water, and then, the solvent is distilled off, and the residue is extracted with ethyl acetate. After distilling off the solvent, the residue is recrystallized from ethyl acetate - n-hexane to give 2-formylaminoindan (19.02 g).

To a solution of the above product (3.22 g) and methyl chloro(methylthio)acetate (3.58 g) in methylene chloride is added dropwise a solution of tin (IV) chloride in methylene chloride under cooling, and the mixture is reacted at room temperature, and thereto is added water. The mixture is extracted with chloroform. The solvent is distilled off from the organic layer, and to the residue are added acetic acid and zinc dust, and the mixture is refluxed. After removing the zinc dust by filtration, the solvent is distilled off. The residue is extracted with ethyl acetate and the solvent is again distilled off to give ethyl (2-formylaminoindan-5-yl)acetate (4.31 g) as colorless oil.

IR ν_{max}^{nujol} cm^{-1}:

3300, 1730, 1660

(2) To a solution of the above product (2.33 g) in methanol is added 1N aqueous sodium hydroxide, and the mixture is reacted at room temperature. The reaction mixture is neutralized with hydrochloric acid and extracted with ethyl acetate. The extract is distilled to remove the solvent, and the residue is recrystallized from ethyl acetate to give (2-formylaminoindan-5-yl)acetic acid (1.50 g).
m.p. 164 - 166°C

Reference Example 2

(2-Benzyloxycarbonylaminoindan-5-yl)acetic acid is obtained in the same manner as described in Reference Example 1 except that benzyloxycarbonyl chloride is used instead of 2M acetic acid-formic acid anhydride.
m.p. 157.5 - 158.5°C

Reference Example 3

(1) To a solution of phenylthioacetic acid (8.14 g) in a mixture of methylene chloride-tetrahydrofuran is added carbonyldiimidazole under ice cooling and the mixture is stirred, and to the reaction mixture are added β-alanine methyl ester hydrochloride (6.98 g) and triethylamine, and the mixture is reacted. After the reaction, the solvent is distilled off under reduced pressure. The residue is extracted with ethyl acetate. The extract is distilled to remove the solvent, and the residue is recrystallized from ethyl acetate - n-hexane to give methyl 3-[(phenylthio)acetylamino]-n-propionate (10.95 g).
m.p. 62 - 63°C

(2) To a solution of the above product (6.35 g) in methylene chloride is added N-chlorosuccinimide (3.50 g), and the mixture is reacted. After the reaction, the solvent is distilled off, and to the residue is added carbon tetrachloride, and the mixture is filtered. The filtrate is concentrated, and the residue is recrystallized from n-hexane to give methyl 3-[chloro(phenylthio)acetylamino]-n-propionate (7.12 g).
m.p. 49 - 52°C

Reference Example 4

Methyl 4-[chloro(phenylthio)acetylamino]-n-butyrate is obtained in the same manner as described in Reference Example 3 except that methyl 4-aminobutyrate is used instead of β-alanine methyl ester.
m.p. 38 - 40°C

alkoxycarbonyl-phenyl group, carboxy-phenyl group, a nitrogen-containing heterocyclic group, a lower alkyl group, or a lower alkyl group having a substituent selected from a lower alkoxycarbonyl group, carboxy group, a lower alkoxycarbonyl-phenyl group, carboxy-phenyl group, a lower alkoxycarbonyl-cycloalkyl group and a carboxy-cycloalkyl group, or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1, wherein R^1 is phenyl group or a phenyl group substituted by a member selected from the group consisting of a lower alkyl group, a lower alkoxy group, a halogen atom, trifluoromethyl, and nitro naphthyl group; or thienyl group, or a pharmaceutically acceptable salt thereof.

3. The compound according to claim 1 or claim 2, wherein R^3 is hydrogen atom or a (C_1-C_5)alkyl group, and R^4 is a (C_3- C_6)cycloalkyl, a (C_2-C_6)alkoxycarbonyl-phenyl group, carboxy-phenyl group, tetrazolyl group, a (C_1-C_5)alkyl group, or a (C_1-C_5)alkyl group having a substituent selected from a (C_2-C_6)alkoxycarbonyl group, carboxy group, a (C_2-C_6)alkoxycarbonyl-phenyl group, carboxy-phenyl group, a (C_2-C_6)alkoxycarbonyl-(C_3-C_6)cycloalkyl group and a carboxy-(C_3-C_6)cycloalkyl group, or a pharmaceutically acceptable salt thereof.

4.The compound according to any preceding claim, wherein R^1 is phenyl, a (C_1-C_5)alkyl-phenyl, a (C_1-C_5)alkoxy-phenyl, a halogenophenyl, trifluoromethylphenyl, nitrophenyl, naphthyl or thienyl, or a pharmaceutically acceptable salt thereof.

5.The compound according to any preceding claim, wherein R^4 is carboxy-phenyl, tetrazolyl, a (C_1-C_3)alkyl, a (C_2-C_4)alkoxycarboxyl-(C_1-C_5)alkyl or a carboxy-(C_1-C_5)alkyl, or a pharmaceutically acceptable salt thereof.

6.The compound according to any preceding claim, wherein R^1 is a (C_1-C_3)alkyl-phenyl, a (C_1-C_3)alkoxy-phenyl, a halogenophenyl, trifluoromethylphenyl, nitrophenyl or naphthyl, or a pharmaceutically acceptable salt thereof.

7.The compound according to any preceding claim, wherein R^1 is methylphenyl, methoxyphenyl, chlorophenyl, bromophenyl, trifluorophenyl, nitrophenyl or naphthyl, or a pharmaceutically acceptable salt thereof.

8.The compound according to any preceding claim, wherein R^3 is hydrogen atom and R^4 is carboxyphenyl a (C_2-C_4)alkoxycarbonyl-(C_1-C_5)alkyl or a carboxy-(C_1-C_5)alkyl, or a pharmaceutically acceptable salt thereof.

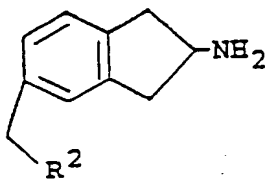
9. The compound according to claim 1, wherein R^1 is halogenophenyl, R^3 is hydrogen atom, and R^4 is carboxy-phenyl, a (C_2-C_4)alkoxycarbonyl-(C_1-C_5)alkyl or a carboxy-(C_1-C_5)alkyl, or a pharmaceutically acceptable salt thereof.

10. The compound according to claim 9, wherein R^1 is chlorophenyl, and R^4 is carboxyphenyl or a carboxy-(C_1-C_4)alkyl, or a pharmaceutically acceptable salt thereof.

11. The compound according to claim 10 which is 3-[[2-[(4-chlorophenyl)sulfonylamino]indan-5-yl]acetylamino]-n-propionic acid, or a pharmaceutically acceptable salt thereof.

12. The compound according to claim 10 which is 4-[[2-[(4-chlorophenyl)sulfonylamino]indan-5-yl]acetylamino]-n-butyric acid, or a pharmaceutically acceptable salt thereof.

13. A compound of the formula:



(II)

wherein R^2 is hydroxymethyl group or a group of the formula:

-CO-N(R^3)-R^4

wherein R^3 is hydrogen atom or a lower alkyl group and R^4 is a cycloalkyl group, a lower alkoxycarbonyl-phenyl group, carboxy-phenyl group, a nitrogen-containing heterocyclic group, a lower alkyl group, or a lower alkyl group having a substituent selected from a lower alkoxycarbonyl group, carboxy group, a lower alkoxycarbonyl-phenyl group, carboxy-phenyl group, a lower alkoxycarbonyl-cycloalkyl group and a carboxy-cycloalkyl group, or a salt thereof.

14. The compound according to claim 13, wherein R^3 is hydrogen atom or a (C_1-C_5)alkyl group, and R^4 is a (C_3-C_6)cycloalkyl, a (C_2-C_6)alkoxycarbonyl-phenyl group, carboxy-phenyl group, tetrazolyl group, a (C_1-C_5)alkyl group, or a (C_1-C_5)alkyl group having a substituent selected from a (C_2-C_6)alkoxycarbonyl group, carboxy group, a (C_2-C_6)alkoxycarbonyl-phenyl group, carboxy-phenyl group, a (C_2-C_6)alkoxycarbonyl-(C_3-C_6)cycloalkyl group and a carboxy-(C_3-C_6)cycloalkyl group, or a salt thereof.

15. The compound according to claim 14, wherein R^2 is a group of the formula:

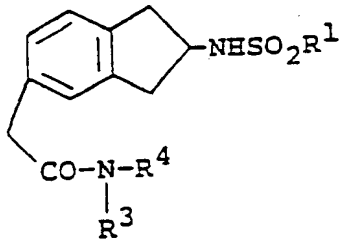
-CO-N(R^3)-R^4

wherein R^1 is as defined above; or

[I]-(C) condensing a compound of the formula (IV) or a reactive derivative thereof with an amine compound of the formula:

R^3-NH-R^4 (V)

wherein R^3 and R^4 are as defined above or a salt thereof to give a compound of the formula (I-b):

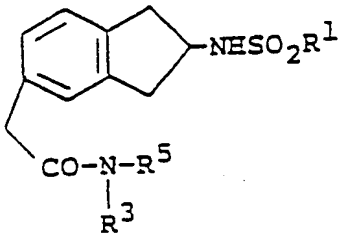


(I-b)

wherein R^1, R^3 and R^4 are as defined above; and

[II] optionally converting the product obtained in the above steps to a pharmaceutically acceptable salt thereof.

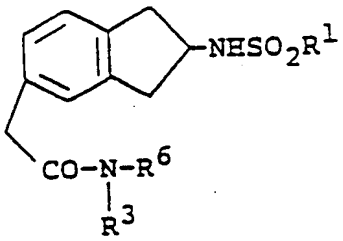
18. A process for preparing an indan derivative of the formula:



(I-c)

wherein R^1 is a substituted or unsubstituted phenyl group, naphthyl group or a sulfur-containing heterocyclic group, R^3 is hydrogen atom or a lower alkyl group and R^5 is carboxy-phenyl group or a lower alkyl group having a substituent selected from carboxy group, carboxy-phenyl group and a carboxy-cycloalkyl group, or a pharmaceutically acceptable salt thereof, which comprises the step(s) of:

[I] hydrolyzing a compound of the formula (I-d):



(I-d)

wherein R^6 is a lower alkoxycarboxy-phenyl group or a lower alkyl group having a substituent selected from a lower alkoxycarbonyl group, a lower alkoxycarbonyl-phenyl group and a lower alkoxycarbonyl-cycloalkyl group, and R^1 and R^3 are as defined above, and

[II] optionally converting the product obtained in the above process to a pharmaceutically acceptable salt thereof.

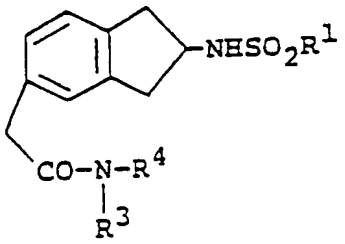
19. A pharmaceutical composition which comprises as an active ingredient an effective amount of the compound as set forth in claim 1 in admixture with a pharmaceutically acceptable carrier or diluent.

20. The pharmaceutical composition according to claim 19, wherein the active ingredient is the compound as set forth in claim 10.

[I]-(C) condensing a compound of the formula (IV) or a reactive derivative thereof with an amine compound of the formula:

R^3-NH-R^4 (V)

wherein R^3 and R^4 are as defined above or a salt thereof to give a compound of the formula (I-b):

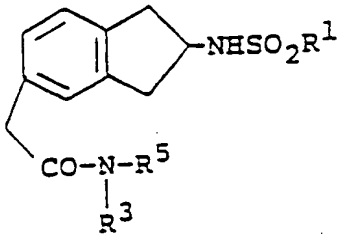


(I-b)

wherein R^1, R^3 and R^4 are as defined above; and

[II] optionally converting the product obtained in the above steps to a pharmaceutically acceptable salt thereof.

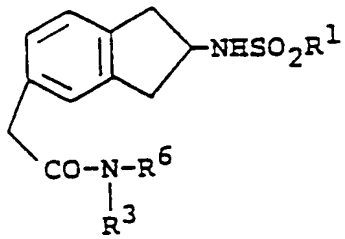
2. A process for preparing an indan derivative of the formula:



(I-c)

wherein R^1 is a substituted or unsubstituted phenyl group, naphthyl group or a sulfur-containing heterocyclic group, R^3 is hydrogen atom or a lower alkyl group and R^5 is carboxy-phenyl group or a lower alkyl group having a substituent selected from carboxy group, carboxy-phenyl group and a carboxy-cycloalkyl group, or a pharmaceutically acceptable salt thereof, which comprises the step(s) of:

[I] hydrolyzing a compound of the formula (I-d):



(I-d)

wherein R^6 is a lower alkoxycarboxy-phenyl group or a lower alkyl group having a substituent selected from a lower alkoxycarbonyl group, a lower alkoxycarbonyl-phenyl group and a lower alkoxycarbonyl-cycloalkyl group, and R^1 and R^3 are as defined above, and

[II] optionally converting the product obtained in the above process to a pharmaceutically acceptable salt thereof.

3. A process as claimed in claim 1 or claim 2, wherein R^1 is phenyl group or a phenyl group substitued by a member selected from the group consisting a lower alkyl group, a lower alkoxy group, a lalogen atom, trifluoromethyl, and nitro; naphthyl group; or thienyl group.

4. A process as claimed in any preceding claim, wherein R^3 is hydrogen atom or a (C_1-C_5)alkyl group, and R^4 is a (C_3-C_6)cycloalkyl, a (C_2-C_6)alkoxycarbonyl-phenyl group, carboxy-phenyl group, tetrazolyl

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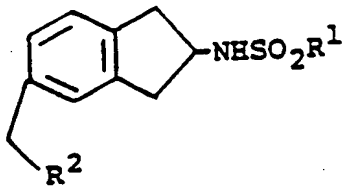
(54) Indan derivatives and process for preparation thereof.

(57) Indan derivatives of the formula:



(I)

wherein R^1 is substituted or unsubstituted phenyl, naphthyl or sulfur-containing heterocyclic group, and R^2 is hydroxymethyl or a group of the formula: -CO- $\underset{\underset{R^3}{|}}{N}-R^4$

wherein R^3 is hydrogen atom or lower alkyl and R^4 is cycloalkyl, lower alkoxycarbonyl-phenyl, carboxy-phenyl, nitrogen-containing heterocyclic group, lower alkyl, or lower alkyl having a substituent selected from lower alkoxycarbonyl, carboxy, lower alkoxycarbonyl-phenyl, carboxy-phenyl, lower alkoxycarbonyl-cycloalkyl and carboxy-cycloalkyl, or a pharmaceutically acceptable salt thereof, which are useful as a platelet aggregation-inhibiting agent and as an agent for the treatment, amelioration and/or prophylaxis of a variety of thrombosis or embolism, coronary and cerebral vascular smooth muscle vellication, asthma, and the like,

EP 0 317 321 A3

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EUROPEAN SEARCH REPORT

Application Number

EP 88 31 0875

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
A	EP-A-0 088 282 (SCHERING AG)		C 07 C 143/78 C 07 C 143/822 C 07 D 257/04 C 07 D 333/34 A 61 K 31/18 A 61 K 31/41 A 61 K 31/38
A	US-A-3 383 414 (W.J. HOULIHAN)		

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

C 07 C 143/00
A 61 K 31/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	21-03-1990	PAUWELS G.R.A.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
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